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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,488	02/12/2004	Adnan M.M. Mjalli	41305-296609	2347

7590 10/29/2009

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EXAMINER	
STOCKTON, LAURA LYNNE	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
10/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,488	MJALLI ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 16, 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-12 and 16-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *July 16, 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4, 7-12 and 16-25 are pending in the application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 16, 2009 has been entered.

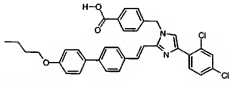
Election/Restrictions

Applicant's election with traverse of Group III (claims 1-46), and the species of Example 320 found on

page 287 of the instant specification (reproduced below), in the reply filed on October 27, 2006 was acknowledged in a previous Office Action.

The structure given in the election was actually the structure of Example 320, as stated by Applicant in the Remarks section of the Amendment filed June 18, 2007.

Example 320



4-[2-[2-(4'-butoxy-biphenyl-4-yl)-(E)-vinyl]-4-(2,4-dichloro-phenyl)-imidazol-1-ylmethyl]-benzoic acid

The requirement was deemed proper and therefore made FINAL in a previous Office Action.

The claims within elected Group III were examined to the extent that they are readable on the elected species of Example 320. Since no prior art was found on the elected species, the examination was previously

expanded within elected Group III. The search and examination within a Markush claim is not further expanded when the expanded subject matter can be rejected under any of 35 USC 101, 102, 103 or 112, first paragraph. Since the expanded subject matter under examination was rejected under 35 USC 112, first paragraph, the examination stopped and the rejection was applied against the claims. Note, M.P.E.P. § 803.02. The subject matter of the previously expanded search (inclusive of the elected species of Example 320) is as follows:

W is $N(R_2)$;

$\mathbf{Ar_1}$ is an optionally substituted phenyl;

$\mathbf{Ar_2}$ is an optionally substituted phenyl;

T is an optionally substituted phenyl;

$\mathbf{L_2}$ is a direct bond; and

all other variables are as defined.

The search has not been further expanded since the claims were not amended in Response to the rejection made in the Office Action of January 26, 2009.

Subject matter not embraced by the above indicated expanded search are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 27, 2006.

Information Disclosure Statement

The Examiner has considered the Information Disclosure Statement filed on July 16, 2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-12 and 16-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutically acceptable salt or prodrug thereof of a compound of formula (I), does not reasonably provide enablement for a solvate of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

a) Determining if a particular compound would form a solvate would require synthesis and recrystallization of the compound solvate using a variety of solvents, temperatures and humidities. The experimentation for solvates is potentially open-ended.

b) The specification merely mentions the Applicant's intention to make solvates, without teaching the preparation thereof.

c) While the claims recite solvates, no working examples show their formation. As stated in *Morton*

International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the formation and actual existence of solvates. Hence, Applicant must show formation of solvates or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of solvates, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of solvates is unpredictable. The Federal Circuit has recognized a solvate as an example of a polymorph or pseudopolymorph (emphasis added):

> "Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005). The same rationale obtains for hydrates; solvates in which the solvent is water. Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), recognize that different polymorphs of the same drug can have different therapeutic activity (emphasis added):

> Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity

> from one form to another may be different. Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.

Further, Vippagunta et al. (Advanced Drug Delivery Reviews, 48 (2001), pages 3-26) state "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated in to the crystal lattice of a compound is complex and difficult." See page 18, section 3.4.

f) The artisan using Applicant's disclosure to prepare the claimed solvates would be, e.g., an experienced process chemist with at least a BS chemistry degree.

g) Chemical reactions are known as unpredictable. *In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971); *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). See above regarding the unpredictability of solvate formation.

h) The breadth of the claims includes thousands of compounds of the instant formula (I) as well as

presently unknown compounds embraced by the terms solvates. See MPEP 2164.01(a), discussed supra, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicant's claimed invention.

Response to Arguments

Applicant's arguments filed July 16, 2009 have been fully considered. Applicant argues that the *Wands* factors are factors that are to be considered to determine whether a claim is enabled and that no one *Wands* factor can be used by itself to assert that a claim is not enabled. Applicant also argues that evidence must be presented asserting why the claims are not enabled.

In response, the *Wands* factors were used to establish that the instant claimed solvates of the compounds of formula (I) were not enabled. See the outline of these factors on pages 5-6 of the Office

Action dated January 26, 2009. Further, evidence was presented in the way of, for example, Vippagunta et al. that raises a question of enablement in making solvates of the instant claimed compounds.

Applicant argues that the Examiner has dismissed the decision in *Ex Parte Gante* because the decision was issued years ago. In response, the Examiner did not dismiss the decision in *Ex Parte Gante* on the bases that the decision was rendered years ago. In *Ex Parte Gante*, the claims were rejected under 35 USC 112, second paragraph, because of the scope of the use of term "solvates" could not be determined. In the instant application, the claims are rejected under 35 USC 112, first paragraph, for lacking enablement of how to make solvates of the instant claimed compounds. The BPAI reversed the Examiner in *Ex Parte Gante* because no evidence was presented that demonstrated that there was a number of inoperative combinations significant enough to force one of ordinary skill in the art to experiment

unduly in order to practice the claimed invention. In the instant case, evidence was presented in the way of, for example, Vippagunta et al., that raises a question of enablement in making solvates of the instant claimed compounds.

Applicant argues that it is well settled law that one need not disclose, and preferably omits that which is well known in the art. Applicant also argues that no acceptable evidence or reasoning that solvates of the presently claimed compounds cannot be made through routine experimentation. Applicant further argues that the Vippagunta et al. reference is ambiguous and cites other review references (Caira, Guillory, Byrn and Morisette - all cited on the IDS filed July 16, 2009) to establish that the making of solvates of a compound is routine and that no undue experimentation is required.

Applicant's arguments have been considered but have not been found persuasive. If it is so routine as

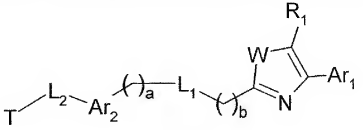
Applicant states, then why aren't any compounds made in the various working examples (over 370 examples disclosed in the instant specification) employing a variety of solvents? The lack of such supports Vippagunta's assertion that it is not predictable which compounds can form solvates. Thus, there is ample evidence to doubt the existence of such compounds for instant compounds.

Applicant argues that: (1) working examples are not required; (2) in *In re Wands*, the production of a monoclonal antibody is much more complex and time-consuming yet the Court in *In re Wands* concluded that it was not excessive and undue; and (3) there are issued patents which have no more description about how to make and use solvates then the presently claimed invention.

Applicant's arguments have been considered but have not been found persuasive. Firstly, there is a presumption of validity in all US patents. The

allowance of claims by the U.S. Patent Office has no relevancy in the consideration of the question of patentability of claims in another case. *In re Greider*, et al., 54 USPQ 139, 1942. It is agreed that working examples are not required in the disclosure. Although, according to MPEP 2164.02, "Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." Further, note that in University of *Rochester v. G.D. Searle & Co.* 68 USPQ2d 1424 at 1438, the screening for over 600 compounds was deemed to be undue. Applicant's scope of compounds of Formula (I) in instant claim 1, reproduced below in-part,

1. (Previously Presented) A compound of Formula (I):



(I)

far exceeds this number. The specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. *In re Gardner*, 166 USPQ 138 (CCPA 1970). Therefore, one skilled in the art could not make the claimed invention without undue experimentation.

Claims 1-4, 7-12 and 16-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutically acceptable salt or prodrug thereof of a compound of formula (I), does not reasonably provide enablement for a solvate of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and thus use the invention commensurate in scope with these claims. Applicant's traverse to this rejection is not persuasive for the following reasons. The Examiner has stated the reason for the rejection is based on evidence in Applicant's own specification of

many examples which consistently failed to produce solvated forms. While it may be routine to make solvates by exposing compounds to a variety of solvents, this does not mean it is routine for any given compound to form solvates - a fact clearly stated by Vippagunta et al. As was stated in *Morton International Inc v. Cardinal Chemical Co.* 28 USPQ2d 1190 at p. 1194: "The specification purports to teach with over fifty examples, the preparation of the claimed compounds with the required connectivity. However… there is no evidence that such compounds exist… the examples of the '881 patent do not produce the postulated compounds..there is… no evidence that such compounds even exist." The same applies in the present case. Applicant urges what is best known can be omitted but the fact remains reacting instant compounds in various solvents, which is the known way to ultimately make solvates, failed to produce solvates. If it is so routine as Applicant states, then why

aren't any compounds made in the various working examples (over 370 examples) employing a variety of solvents? The lack of such supports Vippagunta's assertion that it is not predictable which compounds can form solvates. Thus there is ample evidence to doubt the existence of such compounds for instant compounds. *In re Marzocchi* 169 USPQ 367. Note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative." For all the reasons given above, the rejection is deemed proper and therefore, the rejection is maintained.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the

automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Laura L. Stockton/
Laura L. Stockton
Patent Examiner
Art Unit 1626, Group 1620
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October 29, 2009